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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,693	TABOR ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,24,124-128,130-139,141-155,157-159,161-164 and 170-202* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,24,124-128,130-139,141-155,157-159,161-164 and 170-202* is/are rejected.

7)☒ Claim(s) *1,11,124,137-139,148,170-174,180,187,189,196 and 197* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 23, 2009 has been entered.

Claims 1, 11, 24, 124-128, 130-139, 141-155, 157-159, 161-164, and 170-202 are currently pending. In the response filed on November 23, 2009, Applicant amended claims 1, 11, 24, 132-136, 139, and 148, canceled claims 129, 140, 156, 160, 165, 166, 168, and 169, and added claims 170-202.

Applicant's arguments and the evidence submitted under 37 CFR 1.132 on November 23, 2009 have been fully considered and were sufficient to overcome all of the rejections made previously under 35 U.S.C. 103(a). Accordingly, all of the previously made rejections have been withdrawn (see "Response to Amendment" and "Response to Arguments" section). Upon further consideration, however, new grounds of rejection are made below under 35 U.S.C. 112, first paragraph. New grounds of objection and a new ground of rejection under 35 U.S.C. 112, second paragraph are also applied.

Claim Numbering

2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are

canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claims 182-197, which appear on the last two pages of the claim listing have been renumbered claims 187-202, respectively.

Claim Objections

3. Claim 1 is objected to because of the following informalities: Inserting "double-stranded" before the words "template DNA" is suggested to make clear that the template DNA is a double-stranded molecule since the phrase "wherein....said template DNA molecule does not have a terminal protein covalently bound to either 5' end" implies this. Also, inserting the words "*in vitro*" before the words "reaction mixture" is suggested to make clear that the method is conducted *in vitro*.

Claims 11 and 171-173 are objected to because of the following informalities: A hyphen should be inserted between the words "single" and "stranded".

Claims 124, 174, and 197 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. These claims depend directly or indirectly from claim 1 and require that the method results in 100-fold amplification. However, independent claim 1 already requires 100-fold amplification, and, therefore, claims 124, 174, and 197 are not further limiting.

Claims 137-139 are objected to because of the following informalities: Replacing the words "said accessory protein" in each of these claims with "one of said at least two accessory proteins" is suggested to maintain consistency with claim 1.

Claims 148, 180, and 196 are objected to because of the following informalities: A hyphen should be inserted between the words "single" and "stranded" and between the words "double" and "stranded". Also, inserting the article "a" before "double-stranded exonuclease" and "single-stranded DNA binding protein" is suggested to maintain consistency within the Markush group.

Claims 170, 187, and 189 are objected to because of the following informalities: A hyphen should be inserted between the words "double" and "stranded".

Appropriate correction is required.

Duplicate Claims Warning

4. Applicant is advised that should claim 187 be found allowable, claim 189 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In this case, the two claims are identical.

Claim Rejections - 35 USC § 112, 1st paragraph (Scope of Enablement)

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 11, 24, 124-128, 130-139, 141-155, 157-159, 161-164, and 170-202 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: (i) a method for amplifying a DNA template 150,000-fold comprising incubating the DNA template for 20 minutes at 37°C in an *in vitro* reaction mixture containing potassium glutamate, DMSO, dextran, ATP, CTP, and a UV-treated enzyme mixture comprising wild-type T7 DNA polymerase, Δ28 T7 DNA polymerase, the 63 kDa form of the T7 gene 4 protein, and the single-stranded DNA binding protein from *E. coli*, or (ii) a method for amplifying a DNA template at least 25,000-fold comprising incubating the DNA template for 20 minutes at 37°C in an *in vitro* reaction mixture containing potassium glutamate, DMSO, dextran, ATP, CTP, and a UV-treated enzyme mixture comprising wild-type T7 DNA polymerase, Δ28 T7 DNA polymerase, the 63 kDa form of the T7 gene 4 protein, the single-stranded DNA binding protein from *E. coli,* phosphocreatine, creatine kinase, nucleoside disphosphokinase, inorganic pyrophosphatase, T7 single-stranded DNA binding protein, T7 gene 6 exonuclease, and T7 DNA ligase, does not reasonably provide enablement for a method of amplifying a DNA template at least 100-10,000,000-fold that comprises incubating the template DNA at constant temperature in a reaction mixture comprising: (i) a DNA polymerase and at least two accessory proteins, (ii) a DNA polymerase having a normal level of exonuclease activity, a DNA polymerase having a reduced level of exonuclease activity, a helicase, a primase, and a single-stranded DNA binding

protein, or (iii) wild-type T7 DNA polymerase, a T7 DNA polymerase modified to have a reduced level of exonuclease activity, the 63 kDa form of a T7 gene 4 protein, and a single-stranded DNA binding protein from *E. coli*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention and breadth of the claims

The instant claims are drawn to isothermal methods for amplifying a template DNA molecule without the use of exogenously added oligonucleotide primers. The invention is classified in the unpredictable arts of biochemistry and molecular biology. Independent claim 1 requires obtaining at least 100-fold amplification by incubating the DNA template at a constant temperature in an *in vitro* reaction mixture comprising a DNA polymerase and at least two

accessory proteins. Independent claims 11 and 24 require amplifying a DNA template by at least 10-fold through incubation of the DNA template at a constant temperature in a reaction mixture comprising, in claim 11, a DNA polymerase with a normal level of exonuclease activity, a DNA polymerase modified to have a reduced level of exonuclease activity, a helicase, a primase, and a single-stranded DNA binding protein and, in claim 24, a wild-type T7 DNA polymerase, a T7 DNA polymerase modified to have a reduced level of exonuclease activity, a 63 kDa form of the T7 gene 4 protein, and a single-stranded DNA binding protein from *E. coli*. The dependent claims require higher degrees of amplification and the inclusion of at least one additional reagent, such as an ATP regeneration system, a double-stranded exonuclease, or a ligase.

Claim 1 and those claims dependent therefrom are very broad in scope, because, with the exception of claims 130-136, the claims encompass the use of any type of DNA polymerase, and, with the exception of claims 137-139, the claims encompass the use of any two accessory proteins. Claim 11 and those claims dependent therefrom are also very broad in scope, because the claims encompass the use of a helicase, primase, single-stranded DNA binding protein, and DNA polymerases from any organism. Claim 24 and those claims dependent therefrom are limited to the use of wild-type T7 DNA polymerase, any T7 DNA polymerase modified to have reduced exonuclease activity, any 63 kDa form of a T7 gene 4 protein, and any single-stranded DNA binding protein from *E. coli*, but, like the other currently pending claims, they require attaining very high levels of amplification, specifically at least 10,000,000-fold amplification, using this core enzyme mixture. Finally, only claims 143-147, which depend from claim 1, limit the temperature at which the isothermal amplification reaction is conducted.

Guidance in the Specification and Working Examples

The specification teaches that isothermal amplification of a template DNA can be achieved in the absence of exogenously added primers using a core enzyme mixture consisting of a DNA polymerase, a helicase, a primase, and a single-stranded DNA binding protein (see page 7, for example), but it not clear from the specification as to what levels of amplification are attainable using this minimal enzyme mixture. In other words, the specification does not provide a description of the baseline level of amplification obtainable using the enzyme mixture described as the minimal or core enzyme mixture.

Examples 1, 2, and 8 are most relevant to the claimed methods. In Example 1, which is a prophetic example, the specification teaches that a template DNA molecule **should be capable** of being amplified 150,000-fold by incubating the DNA template for 20 minutes at 37°C in an *in vitro* reaction mixture containing potassium glutamate, DMSO, dextran, ATP, CTP, and a UV-treated enzyme mixture comprising wild-type T7 DNA polymerase, Δ28 T7 DNA polymerase, the 63 kDa form of the T7 gene 4 protein, and the single-stranded DNA binding protein from *E. coli* (pages 21-24). In Example 2, which is also a prophetic example, the specification teaches that the level of amplification **should be** increased to 1,500,000-fold by adding **each of** the following seven reagents to the amplification reaction mixture: (i) phosphocreatine, (ii) creatine kinase, (iii) nucleoside disphosphokinase, (iv) inorganic pyrophosphatase, (v) T7 single-stranded DNA binding protein, (vi) T7 gene 6 exonuclease, and (vii) T7 DNA ligase to the reaction described in Example 1 (pages 24-26). It is not clear from the specification whether the method described in Example 8 was actually conducted, or if this is another working example. The initial description of the method indicates that the example is prophetic, but the conclusion

implies that the experiment was conducted. In Example 8, the specification teaches that a human genomic DNA template can be amplified 25,000-fold using the reaction mixture and procedure described in Example 2 (pages 31-32). This level of amplification is 60-fold lower than the yield disclosed in Example 2, and, therefore, it would appear that there is considerable variability in the level of amplification that can be obtained using the *in vitro* reaction mixture and isothermal amplification conditions described in Example 2. It would also appear that predicting the amplification yield of the many different reaction mixtures encompassed by the claims is highly unpredictable.

It is also noted that neither the specification nor the working examples describes the contribution of the different components of the reaction mixture in isolation or in combination to the level of amplification attained. For example, neither the specification nor the working examples teaches that an inorganic pyrophosphatase and a ligase separately and/or together increase the amplification yield by a particular amount. Also, as noted above, the specification does not describe the level of amplification obtainable using the minimal enzyme mixture comprising a DNA polymerase, helicase, primase, and single-stranded DNA binding protein. Furthermore, neither the specification nor the working examples provide guidance as to the levels of amplification that are possible when the enzyme mixtures comprise polymerases, helicases, and primases from organisms other than the T7 bacteriophage or the effect of the reaction temperature on the amplification yield.

As a result of these deficiencies in the specification, which are not remedied by the prior art, as discussed below, it is virtually impossible for the ordinary artisan to reasonably predict the levels of amplification that will result from any of the claimed reaction mixtures. Since the level

of amplification attainable using the core enzyme mixture (primase, helicase, DNA polymerase, and single-stranded DNA binding protein) has not been determined, it is completely unclear as to: (a) whether the required levels of amplification can be achieved using only the core enzyme mixture, and (b) what degree of improvement results from each of the different additional enzymes and reagents recited in the dependent claims. Also, since the contribution of the different components of the more complicated mixtures described in the working examples to the amplification yield has not been described, it is essentially impossible for the ordinary artisan to reasonably predict the yield of any reaction mixtures other than those described in working examples 1 and 2. However, even these results appear to be associated with unpredictability as evidenced by Example 8.

State of the Prior Art and Unpredictability in the Art

The prior art does not teach a method for isothermally amplifying a template DNA molecule in the absence of exongenously added primers using one of the claimed enzyme mixtures and obtaining a level of amplification within the claimed ranges. The closest prior art is that of Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558; cited previously) and Lee et al. (Molecular Cell (1998) 1: 1001-1010; cited previously). Scherzinger amplified a DNA template molecule 4-fold by incubating the template DNA with a T7 DNA polymerase, T7 DNA-priming protein, and a T7 DNA-binding protein at 30°C for 20 minutes (pages 546 and 549-551). Lee amplified a template DNA molecule 7-fold by incubating the template DNA with a T7 DNA polymerase, the 63 kDa form of the T7 gene 4 protein, which possesses primase and helicase activity, the T7 gene 2.5 protein, which is a single-stranded DNA

binding protein, and potassium glutamate at 30°C for five minutes (pages 1002-1003, 1008-1009, Figure 2, and Figure 3).

The working examples suggest that the claimed methods are unpredictable. As discussed above, Example 2 teaches a reaction mixture that produces 1,500,000-fold amplification of a DNA template. However, Example 8 teaches only 25,000-fold amplification using the same reaction mixture. The reason(s) for this 60-fold difference in amplification yield between the two examples is not discussed, and, therefore, it must be concluded that the amplification yield from a given reaction mixture varies in an unpredictable manner.

The teachings of Jeong et al. (Cell and Molecular Life Sciences (2009) 66(20): 3325-3336; newly cited) also suggest that the claimed methods are associated with a high degree of unpredictability. Jeong teaches that DNA replication systems are highly complex and require the coordinated function of a large number of proteins (page 3331). Jeong further teaches that, as of 2009, only three replication systems, specifically T4, T7, and *E. coli*, have been extensively studied and are known to be useful for *in vitro* nucleic acid amplification methods (page 3331). Jeong describes only one method of isothermal *in vitro* amplification conducted in the absence of exogenously added primers (pages 3330-3331). This reference (Li et al. (Nucleic Acids Research (2008) 36(13): e79; newly cited) describes a primase-based whole genome amplification method that utilizes a reaction mixture and conditions that are very similar to those described in the working examples of the instant application (pages 2-3). Neither Jeong nor Li discusses the contribution of the different reaction components to the amplification yield, which components are minimally required to achieve a particular level of amplification, or the degree to which the proteins from different organisms can be used together in isothermal *in vitro*

amplification methods conducted in the absence of exogenously added primers. Therefore, based on these teachings of Jeong and Li, at the time of the invention (January 1999), it would have been a highly unpredictable undertaking for the ordinary artisan to predict the level of amplification attainable using one of the many reaction mixtures encompassed by the claims under isothermal conditions and in the absence of exogenously added primers. Specifically, this would have been a highly unpredictable undertaking, because relatively few replication systems, which are known to be highly complex, had been extensively studied. As a result, given the complexity of the system, the limited guidance in the prior art, and the inherent unpredictability of multi-component biochemical reaction systems, the ordinary artisan would be unable to reasonably predict the contribution of the different components of the reaction mixture to the amplification yield and the ability of proteins from different organisms to be used together in an in vitro amplification reaction mixture to attain the required levels of amplification without conducting an extensive amount of non-routine experimentation.

Quantity of Experimentation

In this case, a very large quantity of non-routine and unpredictable experimentation would be required of the ordinary artisan to enable the full scope of the claimed methods. Specifically, the ordinary artisan would have to determine, with only limited guidance from the specification and the prior art, which of the large number of reaction mixtures encompassed by the claims are capable of producing the required amplification yields under isothermal conditions and in the absence of exogenously added primers. The contribution of each of the many different reaction components to the amplification yield would have to be assessed in many

different mixtures to obtain the ability to reasonably predict the yield of a particular amplification mixture. The ordinary artisan would also have to determine, through the analysis of many different reaction mixtures, the degree to which proteins from different organisms can be combined in an amplification reaction mixture to produce the required minimum levels of amplification under isothermal conditions and in the absence of exogenously added primers. Since the claims encompass a very large number of diverse reaction mixtures and encompass a wide range of minimum amplification levels, a large quantity of experimentation would be required to obtain the ability to determine which reaction mixtures produce the required degree of amplification. In view of the limited guidance in the specification and the prior art, the ordinary artisan would have to undertake this large quantity of experimentation with only limited guidance and with no guarantee of success. This type of experimentation is considered to constitute undue experimentation.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the claimed methods are broadly drawn to methods for amplifying a template DNA molecule in an isothermal amplification process conducted in the absence of exogenously added primers. Despite the breadth of the claims and the inherent unpredictability in the art, the specification provides only minimal guidance regarding practice of the claimed methods and does not discuss several aspects of the methods

that are critical for successful practice of the full scope of the claimed methods. The prior art does not remedy the deficiencies of the specification, and, therefore, a large quantity of unpredictable experimentation would be required to practice the full scope of the claimed methods. Thus, undue experimentation would be required for the ordinary artisan to practice the full scope of the claimed methods.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 11, 24, 124-128, 130-139, 141-155, 157-159, 161-164, and 170-202 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11, 24, 124-128, 130-139, 141-155, 157-159, 161-164, and 170-202 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

Independent claim 1 is drawn to an isothermal nucleic acid amplification method that comprises amplifying a target nucleic acid at least 100-fold using a reaction mixture comprising any DNA polymerase and any two accessory proteins and lacking exogenously added primers. Claims 130-139, 141-155, 170-179, and 196-202 depend from claim 1. These claims require much higher levels of amplification, specifically up to 10,000,000-fold and further limit the components of the reaction mixture by requiring the inclusion of a specific accessory protein, such as a primase (see claim 138), or another enzyme, such as a pyrophosphatase (claim 150).

The specification teaches at page 7 that the core enzymes in the disclosed reaction mixtures are DNA polymerase, primase, helicase, and single-stranded DNA binding protein, but it does not describe the amplification yields that are attainable using this core enzyme mixture. Neither claim 1 nor any of the claims depending therefrom recite a reaction mixture containing these four enzymes, and, therefore, they appear to be missing essential elements. Also, it would appear that many essential elements are missing from at least claims 124-128, 174-179, and 196-202, because, based on the discussion in working examples 1 and 2, many additional reaction components seem to be required to achieve exponential amplification and the high yields recited in the claims.

Similarly, independent claim 11 is drawn to an isothermal nucleic acid amplification method that comprises amplifying a target nucleic acid at least 10-fold using a reaction mixture that lacks exogenously added primers and comprises any wild-type DNA polymerase, any DNA polymerase modified to have a reduced level of 3'-5' exonuclease activity, any primase, any helicase, and any single-stranded DNA binding protein. Claims 157-159 depend from claim 11. These claims require much higher levels of amplification, specifically up to 10,000,000-fold. The specification teaches at page 7 that the core enzymes in the disclosed reaction mixtures are DNA polymerase, primase, helicase, and single-stranded DNA binding protein, but it does not describe the amplification yields that are attainable using this core enzyme mixture. As a result, it is not clear whether the mixture recited in claim 11 is capable of producing the required amplification yield or if additional elements, which are not currently recited in the claim, are required. Also, it would appear that many essential elements are missing from claims 157-159, because, based on the discussion in working examples 1 and 2, many additional reaction

components seem to be required to achieve exponential amplification and the high yields recited in the claims.

Finally, independent claim 24 is drawn to an isothermal nucleic acid amplification method that comprises amplifying a target nucleic acid at least 10-fold using a reaction mixture that lacks exogenously added primers and comprises wild-type T7 DNA polymerase, any form of the T7 DNA polymerase that has been modified to have a reduced level of 3'-5' exonuclease activity, any 63 kDa version of the T7 gene 4 protein, and a single-stranded DNA binding protein from *E. coli*. Claims 161-164 and 180-195 depend from claim 24. These claims require much higher levels of amplification, specifically up to 10,000,000-fold and further limit the components of the reaction mixture by requiring the inclusion of additional enzymes, such as a double-stranded exonuclease (claim 187), or reagents, such as an ATP regenerating system (claim 180). The specification teaches at page 7 that the core enzymes in the disclosed reaction mixtures are DNA polymerase, primase, helicase, and single-stranded DNA binding protein, but it does not describe the amplification yields that are attainable using this core enzyme mixture. As a result, it is not clear whether the mixture recited in claim 24 is capable of producing the required amplification yield or if additional elements, which are not currently recited in the claim, are required. Also, it would appear that many essential elements are missing from at least claims 161-164 and 180-195, because, based on the discussion in working examples 1 and 2, many additional reaction components seem to be required to achieve exponential amplification and the high yields recited in the claims.

Claim 184 is also indefinite, because there is insufficient antecedent basis for the limitation "said ATP regeneration system". It would appear that perhaps claim 184 was intended to depend from claim 183 rather than claim 173.

Response to Amendment

7. The declaration under 37 CFR 1.132 filed on November 23, 2009 has been fully considered.

Rejections made previously under 35 U.S.C. 103(a)

The declaration is sufficient to overcome all of the rejections made previously under 35 U.S.C. 103(a). Specifically, the following rejections have been withdrawn in view of the declaration filed on November 23, 2009: (1) The rejection of claims 1, 11, 129-139, 141-147, 156, and 165 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, and Tabor, (2) The rejection of claim 24 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, and Bernstein, (3) The rejection of claims 124-128, 157-159, 166, and 168 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, Tabor, and Walker, (4) The rejection of claim 140 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, Tabor, and Bernstein, (5) The rejection of claims 148 and 149 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, Tabor, and Dickinson, (6) The rejection of claims 148 and 150 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, Tabor, and Peller, (7) The rejection of claims 148, 151, and 152 under 35 U.S.C. 103(a) as being

unpatentable in view of the combined teachings of Scherzinger, Sorge, Tabor, and Nakai, (8) The rejection of claims 153 and 154 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, Tabor, and Engler, (9) The rejection of claim 155 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, Tabor, and Jarvis, and (10) The rejection of claims 161-164 and 169 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, Tabor, Bernstein, and Walker.

In point 4 of the declaration, Dr. Tabor, who is one of the inventors named on the instant application, states that, based on the state of knowledge at the time of the invention in the field of replication or amplification conducted isothermally in the absence of exogenous primers, such as Scherzinger, which is representative, the ordinary artisan would not have expected that such amplification reactions could be modified to obtain the high levels of amplification recited in the claims, since Scherzinger only obtained 4-fold amplification.

In points 6-10 of the declaration, Dr. Tabor discusses the differences between two of the references relied upon in all of the previously made rejections - Scherzinger and Sorge. Dr. Tabor states that Scherzinger is concerned with understanding the mechanism of DNA replication and not with nucleic acid amplification, whereas Sorge is concerned with developing efficient amplification methods that utilize exogenous primers. Dr. Tabor states that, since the Scherzinger and Sorge references are directed to completely different goals, the ordinary artisan would not have been motivated to modify the system of Scherzinger to include a modified DNA polymerase, such as the modified polymerase described by Sorge. Dr. Tabor also states that, since the methods of Sorge were conducted with exogenous primers, the ordinary artisan would

not necessarily expect improvement in the yield of the reactions conducted by Scherzinger to the claimed degree.

Dr. Tabor's statements in points 4-10 of the declaration have been carefully considered, and are considered effective to withdraw all of the rejections made previously under 35 U.S.C. 103(a). Briefly, the rejections have been withdrawn, because, as discussed by Dr. Tabor, the ordinary artisan would not have reasonably expected that the system disclosed by Scherzinger could be modified to produce the much higher amplification yields recited in the claims. Also, the ordinary artisan would not have been motivated to combine the teachings of Sorge with those of Scherzinger in view of the very different objectives of the two references.

Presently Applied Rejection under 35 U.S.C. 112, first paragraph

The declaration is insufficient to overcome the rejection of claims 1, 11, 24, 124-128, 130-139, 141-155, 157-159, 161-164, and 170-202 based upon 35 U.S.C. 112, first paragraph (scope of enablement) as set forth above, however.

In point 5 of the declaration, Dr. Tabor states that the ordinary artisan could readily adjust the reaction mixture components using no more than routine experimentation and the guidance set forth in the specification to obtain the very high levels of amplification recited in the claims. As an initial matter, it is noted that the statements in this portion of the declaration are only Dr. Tabor's opinion and are not supported by any factual data or evidence. It is also noted that, as an inventor of the subject matter claimed in the instant application, Dr. Tabor has an interest in the outcome of the case. Dr. Tabor's opinion regarding the ability of the ordinary artisan to practice the full scope of the claimed methods without undue experimentation has been

carefully considered, but it is not persuasive to overcome the scope of enablement rejection set forth above. Briefly, as discussed in the rejection, the specification only describes, via prophetic working examples, the amplification yields that are attainable using two reaction mixtures, which are much more complex and specific than the many different reaction mixtures encompassed by the instant claims. The specification does not describe the contribution of the different reaction mixture components to the amplification yield or the yield attainable using a minimal enzyme mixture consisting of a primase, helicase, single-stranded DNA binding protein, and DNA polymerase, and therefore, it is virtually impossible for the ordinary artisan to predict, without conducting a large amount of non-routine experimentation, the levels of amplification attainable from any reaction mixture encompassed by the claims other than the two reaction mixtures described in the working examples.

Response to Arguments

Applicant's arguments, see pages 13-15, filed on November 23, 2009, regarding the rejection of claims 1, 11, 129-139, 141-147, 156, and 165 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, and Tabor and the rejection of claim 24 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Scherzinger, Sorge, and Bernstein, have been fully considered and are persuasive. Applicant's arguments at pages 13-15 are essentially the same as those presented in the declaration. The rejections have been withdrawn for the reasons discussed above with respect to the declaration.

Since the rejections of claims 124-128, 140, 148-155, 157-159, 161-164, 166, 168, and 169 made previously under 35 U.S.C. 103(a) depend on the primary combination of Scherzinger and Sorge, they have also been withdrawn in view of Applicant's arguments at pages 13-15.

It is noted that some of Applicant's arguments filed on November 23, 2009 pertain to the new rejection under 35 U.S.C. 112, first paragraph (scope of enablement). These arguments have been fully considered, but they were not persuasive. Briefly, Applicant argues that the ordinary artisan would be able to practice the full scope of the claimed methods without undue experimentation using the specification as a guide (pages 15-16). Applicant also notes that the claims as amended contain the elements of working examples 1 and 2 (page 16). Applicant's first argument was not persuasive, because, as discussed above, the specification does not provide guidance as to the components required to achieve the different levels of amplification recited in the claims, the contribution of the different reaction mixture components to the amplification yield, and the ability of proteins from different organisms to be used together. Since the prior art does not remedy these deficiencies in the specification, and since the claimed methods are unpredictable, the specification does not provide an enabling disclosure for the full scope of the claimed methods. Also, it is noted that the claims do not, in fact, contain all of the components present in the reaction mixtures of prophetic examples 1 and 2 as argued by Applicant. Example 1 describes a reaction mixture containing potassium glutamate, DMSO, dextran, ATP, CTP, and a UV-treated enzyme mixture comprising wild-type T7 DNA polymerase, Δ28 T7 DNA polymerase, the 63 kDa form of the T7 gene 4 protein, and the single-stranded DNA binding protein from *E. coli* (pages 21-24), and Example 2 describes a reaction mixture that further comprises each of the following reagents: phosphocreatine, creatine kinase,

nucleoside disphosphokinase, inorganic pyrophosphatase, T7 single-stranded DNA binding protein, T7 gene 6 exonuclease, and T7 DNA ligase (pages 24-26). None of the currently pending claims includes all of these features, which would appear to be required to achieve the required levels of amplification.

It is noted, however, that if an independent claim containing all of the elements of working example 1 or working example 2 was submitted, such a claim would be allowable. Alternatively, Applicant may wish to present additional evidence to establish that the reaction mixture of claim 24, which contains the core enzyme mixture, is, in fact, capable of producing the required level of amplification under isothermal conditions and in the absence of added primers. Such evidence would likely overcome the presently applied rejections under 35 U.S.C. 112, first and second paragraphs. Such evidence should also make clear which additional components, if any, are required to achieve the very high levels of amplification recited in the dependent claims.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Angela M Bertagna/
Examiner, Art Unit 1637

/MP WOODWARD/
Primary Examiner, Art Unit 1637